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EDITORIAL COMMENT

Syncope: Is a Diagnosis a Diagnosis?*

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Syncope is a transient symptom characterized by a sudden loss of consciousness (including by definition concomitant loss of postural tone), with subsequent spontaneous and relatively prompt recovery. Premonitory symptoms may or may not warn of the event. In some cases there are no warning symptoms, or they are lost to recall afterward. Syncope must be differentiated from other conditions in which loss of consciousness may be real or seem to be real, and which thereby mimic "true" syncope. Examples of such conditions include certain types of seizures, sleep disturbances, accidents, and some psychiatric conditions.

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Establishing the basis for syncope (i.e., determining the "diagnosis") is a prerequisite to advising patients with regard to prognosis, and to developing an effective treatment strategy. However, arriving at the diagnosis can be difficult, and is often marked by the undertaking of costly and often fruitless diagnostic procedures. In this regard, the development and evaluation of thoughtful, evidence-based (when possible) diagnostic guidelines/pathways for the evaluation of patients with syncope is highly desirable (1–3). However, because syncope is a temporary state and not a disease, establishing the true value of such pathways is challenging and will likely require careful assessment of outcomes in individual patients. Only then can the diagnosis be validated and the utility of the guideline established. This latter step will remain a hurdle for many years to come.

In this issue of the *Journal*, Garcia-Civera et al. (4) present diagnostic outcomes of an evaluation strategy for patients with syncope. The patients were selected on the basis of the principal criterion that the etiology of the symptoms remained unknown despite an initial evaluation encompassing a medical history and physical examination, 12-lead electrocardiogram (ECG), carotid sinus massage, and 24-h ambulatory ECG monitoring, among other things. Thereafter, the strategy reasonably relied upon certain historical and/or basic testing features in order to determine the subsequent testing direction, an approach similar to that advocated by the European Society of Cardiology Task Force on Syncope (2) and others (5,6) (Table 1).

Among the 184 patients in the report by Garcia-Civera et al. (4), patients with certain findings on initial evaluation, such as structural heart disease, an abnormal ECG, significant arrhythmias on ambulatory monitoring, or palpitations before syncope, underwent clinical electrophysiologic testing as the next step in their assessment. The authors report a 44% diagnostic yield in this group of 72 individuals (i.e., paroxysmal atrioventricular [AV] block in 14, ventricular tachycardia in 9, supraventricular tachycardia in 5, sinus node dysfunction in 3, and carotid sinus syndrome in 1). Further, among 40 patients in whom electrophysiology testing had been nondiagnostic, tilt tests were considered to provide a diagnosis in 23 cases. Finally, of the 17 remaining undiagnosed patients, 15 underwent implantation of an implantable loop recorder (ILR). Two others refused. The ILR provided a positive outcome in 8 of these 15 individuals (i.e., paroxysmal AV block in 3, sinus arrest in 2, polymorphous ventricular tachycardia in 2, and sinus rhythm in 1). Among patients without the above noted initial evaluation features, tilt-table testing was employed as the next step. This test was reported to be diagnostic in 71% of those tested. Overall, among all patients, the investigators report a diagnostic yield of 78%.

POSITIVE TESTS OR APPARENT DIAGNOSTIC OBSERVATIONS: WHAT IS A DIAGNOSIS?

The diagnostic strategy employed by Garcia-Civera et al. (4) is commendable for its organized approach, and is generally consistent with current concepts and published recommendations (1–3). Further, it presents a practicable approach to the "real world" of the syncope evaluation. On the other hand, although integration of a selective ILR strategy with conventional diagnostic procedures such as tilt-table testing and invasive electrophysiologic testing seems defensible, some would argue that a more aggressive ILR implantation strategy is already warranted on the basis of published evidence (2,7).

Perhaps the most important observation presented by Garcia-Civera et al. (4) is that a relatively high diagnostic yield—within the range claimed by other investigators (2,3)—is achievable with a few selected tests. If reproducible, these findings map the way toward minimizing wasteful diagnostic procedures. On the other hand, selection bias could have played a role in the apparent outcome. For example, if the study patients are derived from a referred population, they may have already undergone an element of prestudy screening evaluation by others. If such an evaluation had taken place, and included tests other than simply the basic history, physical examination, and 12-lead ECG, then the total number of procedures needed to make a diagnosis would be underestimated. Future reports should provide a screening log and a detailed description of tests performed. Furthermore, despite the apparent care with which the investigators developed and carried out their evaluation strategy, the validity of

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Table 1. Factors Determining Syncope Diagnostic Evaluation Strategy*

Diagnostic goals
Establish a correlation between symptoms and detected abnormalities
Assess prognosis
Initiate appropriate treatment plan.
Key steps
Obtain *detailed* medical history (including bystanders/relatives)
Identify status of underlying structural heart disease (physical exam, echo)
Factors determining need for further tests
Evidence for structural disease
Certainty of the initial clinical impression
Number and frequency of syncopal events
Family history of syncope or sudden death
Occurence of injury or accident
Patient's occupation, avocation (possible high risk of injury to patient/public)
Ultimate gold standard
Diagnosis-appropriate treatment prevents syncope recurrence during long-term follow-up

*Modified from Benditt DG, Ermis C, Lurie KG, Sakaguchi S. Syncope. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. Evidence Based Cardiology. 2nd edition. London: BMJ Books, 2003:619–33.

the reported diagnostic yield must be considered suspect. There are several reasons for this skepticism.

First, as noted earlier, syncope is not a "disease," the diagnosis of which can be readily confirmed by other tests. In essence, the positive predictive accuracy of a diagnostic test or set of tests cannot be readily assessed in patients with syncope. Because syncope is an episodic symptom, the diagnostic standard remains documentation of an abnormality observed during a spontaneous event. Unfortunately, this is only rarely possible. Consequently, absent concordance of diagnostic laboratory findings and spontaneous documented events (i.e., the gold standard) any abnormality observed during testing must be viewed with suspicion (even if practical necessity demands that it be acted upon). The classic experience of Fujimura et al. (8), and the more recent revelations by Moya et al. (7) in the ISSUE trial and others (9,10) speak to this concern. The former demonstrated the high frequency with which abnormal electrophysiologic laboratory findings are misleading. In essence, Fujimura et al. (8) summarized outcomes of electrophysiologic testing in patients with syncope in whom bradyarrhythmias were known to be the cause of syncope. Among 21 syncopal patients with known symptomatic AV block or sinus pauses, electrophysiologic testing correctly identified only 3 of 8 patients with documented sinus pauses (sensitivity 37.5%) and 2 of 13 patients with documented AV block (sensitivity 15.4%). The ISSUE trial results, on the other hand, amply illustrated the fact that even when pretest conditions pointed in one direction (especially toward a tachyarrhythmia origin), ILRs often revealed something different (usually a bradycardia). In this view, an early ILR strategy was suggested to be safer and more effective than a conventional strategy including electrophysiologic study (11).

Second, apart from the concerns regarding correlation of electrophysiologic findings with real events, the criteria employed by Garcia-Civera et al. (4) for establishing the basis of syncope in the electrophysiology laboratory are at best uncertain. For example, clinical cardiac electrophysiologists are well aware of the historical debate that focused on the clinical relevance of even seemingly straightforward measurements such as the HV interval. In this regard, the authors do not clearly state their diagnostic touchstones, but they do refer to the communication of the European Society of Cardiology Task Force on Syncope Evaluation (1). In their so doing, however, it is crucial for the reader to understand what the task force really said. Careful reading of that cautiously phrased document reveals that the task force members were not totally convinced that indisputable diagnostic criteria had been established. For instance, in regard to sinus node function studies they stated that the CSNRT had to be "very prolonged." Based on examination of the text, it appears that at the very least this implies a duration >800 ms based on the work of Menozzi et al. (12). However, as also clearly stated in the text, such a finding corresponds only to an eightfold increment of syncope risk, and is not an absolute marker of syncope origin. Similar differences of interpretation are clear for other criteria used by the authors, including, for example, the questionable diagnostic importance of an HV interval >70 ms, or an otherwise asymptomatic pause >3,000 ms during carotid sinus massage.

Third, given the limitations of diagnostic testing in the absence of a gold standard, one might argue that in most cases the reliability of a purported diagnosis can only be estimated if, during the course of randomized controlled trials, an apparently diagnosis-appropriate treatment results in fewer syncope recurrences. In several important clinical scenarios, such as acquired complete heart block and syncope associated with life-threatening ventricular tachyarrhythmias, evidence of treatment efficacy (i.e., prevention of syncope recurrences) appears to be adequately substantiated despite absence of randomized controlled trials. On the other hand, in conditions such as neurally mediated vasovagal syncope, the efficacy of current pharmacologic treatments is less certain, and multicenter randomized studies are essential. Further, these multicenter studies must take into account the likelihood (or lack thereof) of a spontaneous untreated recurrence developing during the planned follow-up. Thus, as suggested by Sheldon et al. (13), studies should incorporate individuals with an established history of multiple faints. In many studies, including that of Garcia-Cervia et al. (4), patients qualified for inclusion despite having had relatively few preceding syncope events. In such circumstances, absent extremely long follow-up, the effect of treatment cannot be readily used to verify the diagnosis. To date, with the exception of three recently completed pacing trials in patients with recurrent vasovagal faints (14–16), the evaluation and treatment of syncope has not been the subject of large-scale clinical study using "high recurrence risk" populations. Indeed, the literature on syncope diagnostic testing and treatment is largely composed of case

series, cohort studies, or retrospective analyses of already existing data. For the most part, the impact of testing on guiding therapy and reducing syncope recurrences cannot be discerned from these methods of research. Until randomized controlled studies are undertaken, the true "diagnostic yield" associated with any diagnostic strategy must remain suspect. In other words, a positive test does not a diagnosis make.

Fourth, even the recording of an arrhythmia in conjunction with a spontaneous event may not provide a definitive diagnosis. For instance, asystole of sufficient duration to cause syncope may occur as a result of sinus node dysfunction, or carotid sinus syndrome, or vasovagal syncope, among other things. Establishing the true diagnosis, a necessity in order to discuss prognosis and choose the most appropriate therapy, depends on examining additional layers of what can be a very tough onion.

Finally, the genesis of syncope is often multifactorial, and more than one pathophysiologic factor may contribute to the symptoms. For instance, in the setting of valvular aortic stenosis or left ventricular outflow tract obstruction, syncope is not solely the result of restricted cardiac output, but may be in part due to inappropriate neurally mediated reflex vasodilation and/or primary cardiac arrhythmias (17). Similarly, a neural reflex component (preventing or delaying vasoconstrictor compensation) appears to play an important role when syncope occurs in association with certain brady- and tachyarrhythmias (18–20). Thus, multiple mechanisms should be investigated even when an apparent cause is already detected. This is particularly important for the choice of the most efficacious treatment.

LIMITATIONS OF DIAGNOSTIC TECHNOLOGY

As alluded to earlier, syncope is a transient symptom. Typically patients are most often asymptomatic at the time of evaluation. "Capturing" a spontaneous event during diagnostic testing is uncommon, apart from the case of prolonged ILR monitoring. However, even when it does happen, current technology limits our learning all that we would like to know. Thus, using available ILRs we can obtain ECG recordings during episodic symptom events for considerable periods of time. Nevertheless, even in the case of ILR-documented syncope, we cannot evaluate blood pressure simultaneously, and we cannot obtain a reliable marker of a patient's exertional status at the time of recorded events. Alternatively, we can record blood pressure more or less noninvasively, but we cannot obtain an adequate-quality simultaneous ECG or electroencephalogram. Implantable blood pressure/ECG devices are in development but remain a long way from clinical application. As a result, despite substantial sophisticated technology on our side, the diagnostic evaluation largely remains indirect, and limited to discerning susceptibility to physiologic states that *could cause* loss of consciousness. In essence, the potential *causal relationship* between a diagnostic abnormality and syncope in a given patient is presumptive most of the time. Of necessity, then, there must remain considerable uncertainty regarding the confidence with which "diagnostic" testing results in establishing the most probable cause of symptoms.

A PRACTICABLE "DIAGNOSTIC" STRATEGY

In the evaluation of patients with syncope, the critical first step is the obtaining of a detailed medical history of symptomatic events by an experienced interviewer, including the interviewing of knowledgeable bystanders. The components of the history taking require considerable thought and thoroughness in their own right (2). Next, a physical examination along with certain basic tests (ECG and echocardiogram) should be undertaken to ascertain whether there is evidence of apparently clinically important underlying structural heart disease. In this regard, echocardiography rarely provides a definitive basis for syncope. Nonetheless, the echocardiogram is invaluable given the importance of identifying underlying structural heart disease. Further, in some cases the echocardiogram may provide indirect clues to the cause of syncope if, for example, hypertrophic obstructive cardiomyopathy, severe valvular aortic stenosis, intracardiac tumor (e.g., myxoma), or anomalous origin of one or more coronary arteries is detected. Exercise testing is not often useful, but may be included if syncope occurred with exertion or if ischemic heart disease is suspected. Thereafter, the need for further specialized diagnostic testing will vary depending on various factors, including the certainty of the initial clinical impression, findings during physical examination, the number and frequency of syncopal events reported, the occurrence of injury or accident, and the presence of a family history of syncope or sudden death. Additionally it is important to consider the potential risks associated with the individual's occupation (for example, commercial vehicle driver, machine operator, professional athlete, sign painter, surgeon) or avocation (for example, skier, swimmer) that might be encountered if syncope recurred.

A key point at this phase of the evaluation is the question whether structural heart disease is present or absent. Ignoring the fact that "structural heart disease" is not a term that is readily defined, its absence is widely accepted to exclude for the most part a cardiac cause of syncope. In a recent study (21), heart disease was an independent predictor of cardiac cause of syncope, with a sensitivity of 95% and a specificity of 45%; by contrast, the absence of heart disease allowed exclusion of a cardiac cause of syncope in 97% of the patients. As a rule, if structural heart disease is deemed to be absent, then tilt-table testing and related assessment of autonomic nervous system function are the most useful diagnostic tests to select next. Neurally mediated vasovagal syncope and orthostatic hypotension are by far the most frequent causes of syncope in this setting. On the other hand, if abnormal cardiac findings are identified, their functional significance should be characterized by hemodynamic and/or angiographic assessment as appropriate. Furthermore, because cardiac arrhythmias are a common cause of syncope in the setting of structural cardiac disease,

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assessing the patient's susceptibility to tachy- and bradyarrhythmias by various ambulatory ECG recording techniques (especially wearable or implantable loop recorders) may be warranted. The risk of injury during a spontaneous, albeit recorded, syncope recurrence is a real concern. Ultimately, electrophysiologic testing may be needed, but interpretation of findings must be undertaken with caution for reasons outlined earlier. Although there are no randomized studies, the evidence seems sufficient to indicate that electrophysiologic testing is most likely to be diagnostic in individuals with underlying structural heart disease, and that the induction of reentry supraventricular or monomorphic ventricular tachycardia in a patient with syncope is likely to be significant. These arrhythmias are rarely innocent bystanders. Nonetheless, demonstration of their hemodynamic significance in an individual patient may necessitate their induction with the patient in an appropriately secured upright tilt position. Tilt-table testing would follow if the diagnosis remains in doubt (2). Strong evidence supports the view that specialized neurologic studies are only rarely useful as part of the syncope evaluation (2).

SUMMARY

The ultimate goal of diagnostic testing is to establish a sufficiently strong correlation between syncope and detected abnormalities to permit both an assessment of prognosis and initiation of an appropriate treatment plan. Randomized controlled trials demonstrating that presumptive diagnostic outcomes lead to effective therapy are needed in order to confirm that the detected "cause(s)" of syncope are indeed real.

When it comes to the assessment of syncope, unnecessary and cost-ineffective testing remains an unfortunate feature of current clinical diagnostic practice. Pathways and guidelines offer the potential of helping physicians achieve diagnostic goals in a more expeditious and efficient manner, and studies such as that provided by Garcia-Cervia et al. (4) in this issue of the *Journal* are important in validating their use. However, even in the setting of well-established guidelines, physician expertise in the taking of the medical history and evaluating the pertinent physical findings, and thereby being in a position to select appropriate subsequent testing and interpret test outcomes, varies widely. Ongoing education is needed. An interdisciplinary educational effort incorporating emergency room physicians, general practitioners, internists, pediatricians, neurologists, and cardiologists is essential to bridge this gap. The European Society of Cardiology, through the multinational educational efforts of its Task Force on Syncope, has taken an important step in this direction.

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